REMARKS

Claims 27 and 28 have been amended to clarify the present claimed invention that the inulin and the anti-metabolic anti-cancer drug components are used in combination.

Support for the amendments is found in the original specification, p. 10, line 1 to p. 11, line 12. Furthermore, attention is drawn to the description, p. 10, lines 22-28, from which it follows that if the active components are administered in separate galenic formulations that constitute together the claimed pharmaceutical composition, the administration being made in such a manner that the functional effects of each component are simultaneously present in the human or animal in order to enable the combination to provide its synergistic anti-cancer effect. Pursuant to 37 CFR § 1.121, a marked copy of the amended claims 27 and 28 accompanies this Amendment.

Turning to the continued art rejection, a brief review of the instant invention, and the significant advantages provided thereby may be helpful to the Examiner.

As discussed in the introductory portions of the specification, most anti-cancer drugs have serious disadvantages and drawbacks. They may present a high degree of toxicity for cells of normal body structures which may cause liver or kidney damage. They also may cause increased sensitivity for opportunistic infections, as well as various types of discomfort for the treatment patient, including local necrosis of body structure in which the drug is administered, nausea, vomiting, irritation of the mucoses of the digestive tract and diarrhea, megaloblastosis, and lesions to the liver or digestive tract, such as stomatitis and buccal and gastro-intestinal ulcers. Such disadvantages and drawbacks limit the use of available anti-cancer drugs. Moreover, often a curative effective dose of an anti-cancer drug cannot be given to a patient due

HAYES SOLOWAY P.C.
130 W. CUSHING ST.
TUCSON, AZ 85701
TEL. 520.882.7623
FAX. 520.882.7643

175 CANAL STREET
MANCHESTER, NH 03101
TEL. 603.668.1400
FAX. 603.668.8567

to the too-high toxicity of the drug to normal cells or to the too-high degree of discomfort caused to the patient by the drug.

The present invention provides an improvement in treating cancer using anti-metabolic anti-cancer drugs by continuing with the treatment regimen inulin, which combination results in a synergistic anti-cancer effect. As a result, the therapeutic effect of the anti-cancer drug is significantly increased permitting better control of disease and/or the use of reduced concentrations of anti-cancer drugs, which may result in reduced adverse side effects, while still maintaining the same or desired therapeutic effect.

In rejecting the claims as anticipated by EPO 0 692 252 (B1), the Examiner takes the position that the synergistic property of the claimed combination is an inherent property of the disclosed combination. However, as argued in Amendment A, which is incorporated by reference, the '252 EP Patent does not disclose the claimed combination. Rather, EP '252 at best teaches a combination of inulin and an anti-mitotic drug. More particularly, EP '252 teaches the use of inulin and oligofructose for the manufacture of a medicament for the prevention of mammary carcinogenesis and for the treatment of breast cancer. EP '252 further discloses on page 3, lines 5-7, that said medicament may also comprise conventional chemotherapeutic products indicated on pages 249-253 of the "Répertoire Commenté des Médicaments" (1989) (document already on file; see Information Disclosure Statement of January 9, 2001, page 1). On the basis of the mechanism of their activity, chemotherapeutic products are classified in several well-defined classes. These classes, together with a few examples of products for each of said classes, are listed in the "Répertoire Commenté" (*o.c.*) and are also indicated in EP '252 (page 3, lines 8-20).

HAYES SOLOWAY P.C.
130 W. CUSHING ST.
TUCSON, AZ 85701
TEL. 520.882.7623
FAX. 520.882.7643

175 CANAL STREET
MANCHESTER, NH 03101
TEL. 603.668.1400
FAX. 603.668.8567

In Example 7 of EP '252 (page 10, lines 41-47) it is mentioned that "to determine [potential] synergistic therapeutic effect, a pharmaceutical composition comprising RAFTILINE® (trade name for chicory inulin of ORAFTI, Tienen (Belgium)) and a conventional chemotherapeutic product actively destroying malignant tumour cells is prepared," and a test is described wherein doxorubicine (an anti-cancer drug of the class of antimitotic antibiotics (see description, p. 2, line 22)) is injected into mice fed with oligofructose/RAFTILINE® that were previously inoculated with L1210 leukaemic tumor cells. This mention of a combination of inulin and doxorubicine is the only pharmaceutical composition comprising inulin and a chemotherapeutic product that is substantiated in EP '252. However, EP '252 is completely silent about the outcome of the test and about a possible synergistic anti-cancer effect between inulin and said doxorubicine.

Thus, contrary to the remark made in the Office Action (p. 2), the prior art (EP '252) does not disclose a combination of inulin/oligofructose and "an anti-metabolic drug," but rather discloses a combination of inulin/oligofructose and an "anti-mitotic antibiotic," being the only substantiated combination of inulin/oligofructose and a chemotherapeutic product disclosed in EP '252. Based upon the disclosures of the "Répertoire Commenté des Médicaments" (1989), anti-metabolic drugs and anti-mitotic antibiotics belong to clearly different classes of chemotherapeutic products. Thus, contrary to the allegation in the Office Action (p. 2), the claims of the subject Application, which specifically read only on a combination of inulin/oligofructose and "an anti-metabolic drug," do not read at all on a composition of the prior art.

HAYES SOLOWAY P.C.
130 W. CUSHING ST.
TUCSON, AZ 85701
TEL. 520.882.7623
FAX. 520.882.7643

175 CANAL STREET
MANCHESTER, NH 03101
TEL. 603.668.1400
FAX. 603.668.8567

The disclosure of EP '252, p. 3, lines 5-7, mentions that a medicament for the treatment of breast cancer containing inulin or oligofructose may in addition comprise conventional chemotherapeutic products described on pages 249-253 of the "Répertoire Commenté des Médicaments" (1989), at best can be read on a possible composition that is merely seeking the addition of the effects of inulin/oligofructose and of a chemotherapeutic product, but is non-enabling with respect to the claimed compositions of the subject invention that present a synergistic anti-cancer effect. Indeed, out of the high number of possible combinations of inulin/oligofructose and a chemotherapeutic product, only one specific combination is disclosed (combination of inulin/oligofructose and an anti-mitotic antibiotic product (Example 7, page 10)), but no combination of inulin/oligofructose and an anti-metabolic drug is substantiated or disclosed; no teaching is given about the manner to select a particular combination that would present a synergistic anti-cancer effect; and, no evidence is given of a possible synergistic effect of a combination of inulin/oligofructose and a chemotherapeutic product, *a fortiori* no evidence or teaching is given about a possible synergistic effect of a combination of inulin/oligofructose and an anti-metabolic chemotherapeutic product.

Accordingly, in view of the above comments, the composition of the current main claim (claim 21), which relates to a combination of inulin and an anti-metabolic anti-cancer drug (a specific class of chemotherapeutic products that is clearly different from the class of antimitotic antibiotics), has thus to be considered both novel and non-obvious in view of EP '252.

Moreover, from the prior art (Leibovici, et al., 1983; see description p. 6, line 35 to p. 7, line 4), it follows that synergistic anti-cancer effect between the fructan levan and a cytotoxic (chemotherapeutic) product was only observed for the particular combination of levan and

HAYES SOLOWAY P.C.
130 W. CUSHING ST.
TUCSON, AZ 85701
TEL. 520.882.7623
FAX. 520.882.7643

175 CANAL STREET
MANCHESTER, NH 03101
TEL. 603.668.1400
FAX. 603.668.8567

methotrexate (an anti-metabolic drug) and this with respect to a particular kind of cancer (Lewis lung carcinoma), and that said synergistic effect is even not provided by a combination of said levan and another compound from the same class of chemotherapeutic products, namely the anti-metabolic 5-fluoro-uracil). Because Leibovici et al. only reads on compositions containing a combination of levan and a chemotherapeutic product, the composition of the present invention is clearly novel over Leibovici et al.

As noted in the paragraph bridging pages 5-6 of Applicants' specification, inulin is essentially non-digestible, and therefore generally considered as "soluble dietary fibers." Thus, it must be considered unobvious that combining inulin, an essentially non-digestible fiber supplement, with a specific class of anti-metabolic anti-cancer drugs would result in a synergistic effect or potentiation of the anti-cancer effect of the anti-cancer drug. Thus, not only is Applicants' claimed invention novel, it is unobvious.

Furthermore, on the basis of the prior art, including EP '252 and Leibovici et al., and particularly in view of the uncertainty and unpredictability of the effect of pharmaceutical compositions on living organisms, one skilled in the art could not predict or expect that a particular combination of inulin/oligofructose and a particular class of chemotherapeutic products would present a synergistic anti-cancer effect. This is furthermore evidenced by the experimental data presented in Table 1, p. 14 of the description. These data clearly support the claimed criticality to the synergistic anti-cancer effect of the claimed combination of inulin and an anti-metabolic drug.

In the Remarks, the Examiner mentions that the specification is not commensurate in scope with the claim language. It is not clear whether the Examiner means to raise a § 112

HAYES SOLOWAY P.C.
130 W. CUSHING ST.
TUCSON, AZ 85701
TEL. 520.882.7623
FAX. 520.882.7643

175 CANAL STREET
MANCHESTER, NH 03101
TEL. 603.668.1400
FAX. 603.668.8567

rejection at this stage of the prosecution. However, Applicants note that the claimed synergistic anti-cancer effect is not limited to the combination of inulin/oligofructose and a particular anti-metabolic anti-cancer drug (5-fluoro-uracil), but is also provided by the combination of inulin/oligofructose and another anti-metabolic anti-cancer drug, *in casu* methotrexate.

In contrast with Leibovici et al. *o.c.*, Applicants have proven that the synergistic anti-cancer effect of the combination of inulin/oligofructose and an anti-metabolic anti-cancer drug is not limited to one single anti-metabolic anti-cancer drug, Applicants submit that, having supported the claimed pharmaceutical composition by two examples, their claims to a combination of inulin/oligofructose and a drug from the specific and defined class of anti-metabolic anti-cancer drugs satisfy the requirements of 35 USC § 112 and 35 USC § 101.

The foregoing Amendment makes no claim changes that would require further search by the Examiner. Accordingly, entry of the foregoing Amendment and allowance of the Application are respectfully requested.

In the event there are any fee deficiencies or additional fees are payable, please charge them (or credit any overpayment) to our Deposit Account No. 08-1391.

Respectfully submitted,

Norman P. Soloway
Attorney for Applicants
Reg. No. 24,315

HAYES SOLOWAY P.C.
130 W. CUSHING ST.
TUCSON, AZ 85701
TEL. 520.882.7623
FAX. 520.882.7643

175 CANAL STREET
MANCHESTER, NH 03101
TEL. 603.668.1400
FAX. 603.668.8567

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I hereby certify that this correspondence is being sent via facsimile to EXAMINER ZOHREH A. FAY of the United States Patent and Trademark Office at facsimile number (703) 872-9307, on February 3, 2003 from Tucson, Arizona.

By: Nigel Mohalane

MARKED CLAIMS SHOWING CHANGES MADE

27. (Twice Amended) Pharmaceutical composition according to claim 21, in which the inulin and the anti-metabolic anti-cancer drug which constitute the combination are [simultaneously] present in the same galenic formulation.

28. (Twice Amended) Pharmaceutical composition according to claim 21, in which the inulin and the anti-metabolic anti-cancer drug which constitute the combination are present in separate galenic formulations which in combination together form the pharmaceutical composition.